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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,549	07/27/2001	Rainer H. Muller	662-57773	7384

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MANELLI DENISON & SELTER
2000 M STREET NW SUITE 700
WASHINGTON, DC 20036-3307

EXAMINER
SHEIKH, HUMERA N

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 09/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/915,549	MULLER, RAINER H.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,19-66,143,144,146 and 148-150* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,19-66,143,144,146 and 148-150* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Receipt of the request for extension of time (3 months) and the Amendment, both filed 07/09/03 is acknowledged.

The 35 U.S.C. 112 second paragraph rejections have been *withdrawn*.

Claims 1-15, 19-66, 143, 144, 146 and 148-150 are pending. Claim 24 has been amended. New claims 149-150 have been added. Claims 1-15, 19-66, 143, 144, 146 and 148-150 are rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144, 146 and 148 are rejected under 35 U.S.C. 102(b) as being anticipated by *Davis* (EPO 0 296 845).

Davis discloses a dispersion comprising an oil-in-water emulsion containing a poorly soluble active ingredient (antifungal - Amphotericin B), wherein the emulsions are

administered parenterally (i.e., intravenously, subcutaneously, intramuscularly) (see reference columns 2 line 15 through col. 4, line 35).

Claims 1-11, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144, 146 and 148 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaufman *et al.* (US Pat. No. 5,616,330).

Kaufman discloses stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract); (col. 1, line 64 through col. 2, line 60).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 19-66, 143, 144, 146 and 148-150 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Davis* (EPO 0 296 845) alone *or* Kaufman et al. (US Pat. No. 5,616,330) alone.

Davis teaches a dispersion comprising an oil-in-water emulsion containing a poorly soluble active ingredient (antifungal - Amphotericin B), wherein the emulsions are administered parenterally (i.e., intravenously, subcutaneously, intramuscularly) (see reference columns 2 line 15 through col. 4, line 35). The emulsions are stable and reduce the toxicity of the drug. Davis teaches that the invention provides an oil-in-water surfactant-stabilized emulsion of a drug, wherein the drug is poorly soluble in both oil and water (col. 2, lines 15-19).

The drug used in this instance is the antibiotic, Amphotericin B. However, the drug may be any selected from a general or local anesthetic, hypnotic, sedative, antibiotic or anti-microbial, anti-neoplastics or immunosuppresants (col. 3, lines 3-19). The surfactant used is preferably lecithin or phosphatidyl choline. The amount of surfactant used may be from 0.5 to 10% (col. 4, lines 10-12). This range clearly meets the applicant's claimed amount of less than 15 wt.%. The amount of oil in the final emulsion taught is suitably 5% to 50%. Any pharmaceutically acceptable oil may be

used, for example, soybean or safflower oil or medium chain triglycerides or monoglycerides (col. 4, lines 3-9). The level of drug can be up to 1mg/ml, in the case of Amphotericin B.

The emulsions are usually administered parentally, for example by continuous venous infusion or by injection, which may be intravenous, subcutaneous or intramuscular (col. 4, lines 19-31). The examples demonstrate the teachings of emulsions using Amphotericin B in various conditions. For instance, Example 1 demonstrates an intravenous emulsion with amphotericin B (50 mg), wherein the drug was dissolved in methanol (100 ml). The oil used in this case was soya oil (10 ml) and the emulsifier used was (1.2 g) egg phosphatidylcholine dispersed in 90 ml water. Other suitable emulsifiers can also be used, such as poloxamer, poloxamine series (col. 5, line 30 through col. 6, line 21). Example 3 shows emulsions of amphotericin B resulting in a small particle size of less than 200 nm average diameters. Similarly, Example 5, demonstrates emulsion droplet sizes, measured by a laser diffraction sizer, wherein majority of droplets were less than 1 micron diameter (col. 7, line 20 through col. 8, line 46).

The instant invention is drawn to a dispersion which comprises an oily phase; an aqueous phase, in the form of an oil-in-water emulsion and at least one active ingredient that is slightly or poorly soluble in the oily and aqueous phase, wherein the dispersion is free from toxicologically dangerous solvents.

Davis explicitly teaches a dispersion comprising an oil-in-water emulsion comprising a poorly soluble drug (Amphotericin B), which is administered parenterally,

as similarly desired by the applicant. There is no significant distinction observed between the prior art and the instant invention since the prior art teaches the applicant's claimed desired objectives of a dispersion comprising an oil-in-water emulsion administered intravenously.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Davis, who teaches an oil-in-water emulsion administered parenterally, comprising a poorly soluble drug (Amphotericin B) because Davis that the emulsions are stable and reduce the toxicity of the drug. The expected result would be an improved stable dispersion for the beneficial treatment of infectious conditions.

Regarding the instantly claimed amounts, Davis teaches similar amounts and percentages as desired by the applicant. Furthermore, it would have been obvious to one of ordinary skill in the art that suitable amounts and percentages could be determined through the use of routine or manipulative experimentation. Additionally and in the absence of showing any criticality, the applicant has not shown any unexpected results that accrue from the use of the instantly claimed amounts. The prior art teaches suitable concentrations to arrive at stable emulsions.

Kaufman teaches stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract); (col. 1, line 64 through col. 2, line 60). The oil-in-water emulsion system includes a taxine, oil, water and a surfactant. More particularly,

a taxine, such as taxol is solubilized in the oil in an effective pharmaceutical amount for intravenous administration. The taxine and oil mixture forms a dispersed phase in the water. Other taxines include taxotere, spicatin and others (col. 2, lines 3-8). Kaufman teaches that the oil may be any of a number of oils, such as mineral, vegetable, animal, essential and synthetic oils, hydrocarbons, paraffin oils or mixtures thereof. Preferably the oil is rich in triglycerides, such as safflower oil, soybean oil or mixtures thereof. Because taxol is more soluble in safflower oil than soybean oil, safflower oil is most preferred (col. 2, lines 10-15). The surfactant used may be a number of surfactants, and is usually a phospholipid, such as lecithin (col. 2, lines 15-17). The surfactant is needed to form stable emulsions.

Kaufman teaches that typically the taxine is present in an amount of about 0.1% to about 1% by weight of the emulsion. The oil is present in an amount of from about 1% to about 40% and the surfactant is present in an amount of about 0.5% to about 5% by weight of the emulsion. These ranges clearly read on the applicant's specified ranges.

The composition may also include further additives, such as glycerin, xylitol, mannitol, dextrose, Ringer's solution and sterols (col. 2, lines 23-36).

The examples demonstrate various preparations of emulsions comprising taxol. Example 1 shows results of a safflower oil solution containing 15 mg taxol/ml and 20 mg cholesterol/ml. This resulting composition is shown in Table 1. The particular ingredients used were lecithin, safflower oil, glycerin, cholesterol and taxol. Similarly, Example 2 shows the results for five different taxol formulations, wherein the mean

particle sizes obtained were less than 1 nm, respectively (col. 4, line 47 through col. 6, line 46). In addition, the particle size was relatively constant over time, which further demonstrated the stability of the lipid emulsions of taxol.

The instant invention is drawn to dispersion which comprises an oily phase; an aqueous phase, in the form of an oil-in-water emulsion and at least one active ingredient that is slightly or poorly soluble in the oily and aqueous phase, wherein the dispersion is free from toxicologically dangerous solvents.

Kaufman teaches stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract). There is no significant distinction observed between the prior art and the instant invention since the prior art teaches the applicant's claimed desired objectives of a dispersion comprising an oil-in-water emulsion administered intravenously.

Furthermore, the applicant has not demonstrated any unexpected results that accrue from the instantly claimed percentages or ranges. The prior art teaches similar amounts using the same composition.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Kaufman, who teaches an oil-in-water emulsion administered for intravenous administration, comprising a poorly soluble drug (taxol) because, Kaufman teaches that such a composition would exhibit minimal side effects and successfully overcome the previous deficiencies of the prior art. The

expected result would be a stabilized oil-in-water emulsion for administering taxol intravenously.

This rejection is maintained and applied to newly added claims 149 & 150.

Davis teaches a dispersion comprising an oil-in-water emulsion containing a poorly soluble active ingredient (antifungal - Amphotericin B), wherein the emulsions are administered parenterally (i.e., intravenously, subcutaneously, intramuscularly) (see reference columns 2 line 15 through col. 4, line 35). The emulsions are stable and reduce the toxicity of the drug. The oil-in-water surfactant-stabilized emulsion contains a surfactant in an amount of from 0.5 to 10% (instant claims require 0.1% - 20%).

Kaufmann teaches stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract); (col. 1, line 64 through col. 2, line 60). The oil-in-water emulsion system includes a taxine, oil, water and a surfactant. The amount of surfactant contained in amounts of from about 0.5% to about 5%. Kaufmann teaches that the surfactant is needed to form stable emulsions.

The prior art teaches the generic concept of providing emulsions comprising poorly soluble active ingredients in stable form for intravenous administration.

Response to Arguments

Applicant's arguments filed 07/09/03 have been fully considered but they are not persuasive.

Firstly, the applicant argued, "The present invention does not use organic solvents and is organic solvent-free. Kaufmann contains organic solvent residues."

This argument has been fully considered, but was not found to be persuasive. Kaufmann discloses stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (col. 1, line 64 through col. 2, line 60). The oil-in-water emulsion system includes a taxine, oil, water and a surfactant. The applicant's argument that organic solvents are not excluded in Kaufmann was not found to be persuasive since one of ordinary skill in the art would be able to determine acceptable or suitable solvents and one of ordinary skill would be able to differentiate between ingredients that may or may not be detrimental to the formulation itself. Since Kaufmann utilizes pharmaceutically acceptable solvents in a stable oil-in-water emulsion and also teaches that his formulation provides for a stable emulsion having minimal side effects, it would be recognized that these solvents would not, in effect or nature, be toxicologically dangerous to the formulation. Furthermore, the examiner notes that the instant claims use "comprising" claim language, and hence permits the use of additional components asides from those recited in the claims.

Secondly, the applicant argued regarding the 35 U.S.C. 102() rejection over Davis (EP '845) stating, "Davis uses organic solvents and always contains solvent residues, whereas the product of the invention is organic solvent-free because no organic solvents are used in the production process. The present invention allows the incorporation of the drug beyond the concentration soluble in the oil and water phase of the emulsion; supersaturated emulsions are created, which are not disclosed in Davis. On the contrary, Davis teaches clear limits for the maximum drug incorporation."

These arguments have been fully considered, but were not found to be persuasive. Davis discloses a dispersion comprising an oil-in-water emulsion containing a poorly soluble active ingredient (antifungal - Amphotericin B), wherein the emulsions are administered parenterally (i.e., intravenously, subcutaneously, intramuscularly) (column 2 line 15 through col. 4, line 35). The emulsions are stable and reduce the toxicity of the drug. Davis teaches that the invention provides an oil-in-water surfactant-stabilized emulsion of a drug, wherein the drug is poorly soluble in both oil and water (col. 2, lines 15-19). The applicants argument that the instant invention allows the incorporation of the drug beyond the concentration soluble in the oil and water phase of the emulsion was not found to be persuasive, since Davis explicitly teaches emulsions that are stable and reduce the toxicity of the drug. Furthermore, Davis also teaches removing at least most of any co-solvent that is present. Additionally, one of ordinary skill in the art would be able to determine suitable solvents, which would not be deemed detrimental to the formulation itself. Furthermore, the applicant's arguments that 'no organic solvents are used in the production process' is

not persuasive since the instant pending claims are composition claims and it is the patentability of the composition itself that must be established. Davis teaches a similar composition for a similar intended purpose as the applicants. The applicants arguments regarding the maximum concentrations of drug being soluble are also not persuasive, since, generally, differences in concentration (or temperature) will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration (or temperature) is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). The prior art clearly recognizes the generic concept of formulating a stable oil-in-water emulsion comprising poorly soluble active ingredients.

Next, the applicant argued regarding the 35 U.S.C. 102(b) rejection over Kaufmann ('330) stating, "Kaufmann also uses organic solvents to dissolve the drug, which means the emulsion will also have at least residues of organic solvents. Kaufmann does not teach a super-saturated emulsion. The present invention can go beyond the maximum concentration soluble in the oil phase to provide a supersaturated concentration range."

These arguments have been fully considered, but were not found to be persuasive. The teachings of Kaufmann have been delineated above. Kaufmann discloses stable oil-in-water emulsions for intravenous administration incorporating a

poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water. It is deemed obvious to one of ordinary skill in the art to effectively distinguish between ingredients that may or may not be detrimental to the formulation itself. Since Kaufmann utilizes pharmaceutically acceptable solvents in a stable oil-in-water emulsion and also teaches that his formulation provides for a stable emulsion having minimal side effects, it would be recognized that these solvents would not, in effect or nature, be toxicologically dangerous to the formulation. Hence, the applicants arguments that solvents are incorporated in the invention of Kaufmann is not persuasive. The applicants arguments regarding the maximum concentrations of drug being soluble are also not persuasive, since, generally, differences in concentration (or temperature) will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration (or temperature) is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." The prior art clearly recognizes formulations of stable oil-in-water emulsions, which comprise poorly soluble active ingredients and therefore, the incorporation of solvents would not adversely affect the composition.

Lastly, the applicant argued regarding the 35 U.S.C. 103(a) rejections over Davis or Kaufmann stating, "Davis does not teach supersaturation of drugs. The prior art concentrations are not sufficiently high enough to obtain acceptable injection volumes."

These arguments have been fully considered, but were not found to be persuasive. Davis teaches an oil-in-water emulsion which provides long-term stability. It is the patentability of the composition, per se that must be established. Davis recognizes the concept of intravenous delivery of poorly soluble drugs and teaches the effective delivery of non-toxic amounts of the emulsion. One of ordinary skill in the art would be able to determine suitable saturation concentrations through the use of routine or manipulative experimentation, based on the intended purpose, since these are viewed as variable parameters.

The applicant also argued regarding Kaufmann stating, "Kaufmann is working with an oil phase at the maximum solubility, whereas the instant invention is working well above the saturation solubilities. The present invention is a supersaturated system. Furthermore, there is no teaching in either reference to exclude the use of organic solvents."

These arguments have been considered, but were not persuasive. The teachings of Kaufmann have been discussed above. Kaufmann teaches stable oil-in-water emulsions for poorly soluble active ingredients. The applicant's arguments that there is no teaching in either reference to exclude the use of organic solvents is not persuasive since the instant claims use 'comprising" claim language, and thus the incorporation of additional ingredients, asides from those recited are not excluded from the claims. The prior art teaches stable emulsions incorporating solvents, however, since these solvents are routinely used in the pharmaceutical art, they would not be

considered detrimental or toxic to the formulation. Hence, the instant invention is rendered obvious and unpatentable over the prior art.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Prior Art made of record and deemed relevant by the examiner:

US Pat. No. 5,651,991 Sugiyama et al. (07/1997)

US Pat. No. 5,534,502 Seki et al. (07/1996)

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (703) 308-4429. The examiner can normally be reached on Monday through Friday from 7:00A.M. to 4:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Hns
September 08, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600